Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container

(bimatoprost)

UK Licence No: PL 35533/0128

Aspire Pharma Ltd

LAY SUMMARY

Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container (bimatoprost)

This is a summary of the Public Assessment Report (PAR) for Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container (PL 35533/0128). It explains how Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For ease of reading, this medicinal product will be referred to as Bimatoprost eye drops throughout the Lay Summary.

For practical information about using Bimatoprost eye drops, patients should read the package leaflet or contact their doctor or pharmacist.

What is Bimatoprost eye drops and what is it used for?
Bimatoprost eye drops is a 'hybrid medicine'. This means that it is similar to a reference medicine, Lumigan 0.3 mg/ml eye drops, solution, single dose container (Allergan Pharmaceuticals Ireland) containing the same active substance.

Bimatoprost eye drops is an anti-glaucoma preparation which is used to reduce high pressure in the eye. If the high pressure is not reduced, it could lead to a disease called glaucoma and eventually damage the sight. This medicine may be used on its own or with other drops called beta-blockers which also reduce pressure.

How do Bimatoprost eye drops work?
Bimatoprost eye drops contains the active ingredient bimatoprost, which belongs to a group of medicines called prostamides. The eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up. This medicine works by increasing the amount of liquid that is drained as a result reduces the pressure inside the eye.

How is Bimatoprost eye drops used?
The pharmaceutical form of this medicine is an eye drop, solution and the route of administration is for use in the eye (ocular use).

The patient should always use this medicine exactly as their doctor has told them. They should check with their doctor or pharmacist if they are not sure.

The recommended dose is one drop once daily in the affected eye(s).

If patients are using Bimatoprost eye drops with another eye drop, the drops should be administered at least 5 minutes apart.

Patients must not use the eye drop more than once a day as the effectiveness of treatment may be reduced.

After putting the drop into the eye(s), patients must throw away the used single-dose container even if there is solution remaining to avoid contamination of the preservative free solution.

The remaining containers must be stored in the sachet and should be used within 7 days after opening of

the sachet. If there are any containers left 7 days after opening the sachet they should be safely thrown away and a fresh sachet must be opened. It is important to continue to use the eye drops as prescribed by a doctor.

Patients who wear contact lenses must take their lenses out before using this medicine and must also wait 15 minutes after using the drops before they put the lenses back in.

This medicine can only be obtained with a prescription.

For further information on how Bimatoprost eye drops is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Bimatoprost eye drops have been shown in studies?
Because Bimatoprost eye drops is a hybrid application and is considered to be therapeutically equivalent to the reference product, Lumigan 0.3 mg/ml eye drops, solution, single dose container, its benefits and risks are taken as being the same as those of the reference medicine.

What are the possible side effects from Bimatoprost eye drops?
The most common side effect with Bimatoprost eye drops (which may affect more than 1 in 10 people) is slight redness (up to 24% of people).

The common side effects with Bimatoprost eye drops (which may affect up to 1 in 10 people) are small breaks in the surface of the eye, with or without inflammation, irritation, itchy eyes, pain, dryness, a feeling that something is in the eye, longer eyelashes, darker skin colour around the eye and red eyelids.

For the full list of all side effects reported with Bimatoprost eye drops, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Bimatoprost eye drops approved?
The MHRA decided that Bimatoprost eye drops's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Bimatoprost eye drops?
A risk management plan has been developed to ensure that Bimatoprost eye drops is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Bimatoprost eye drops, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Bimatoprost eye drops
A Marketing Authorisation was granted in the UK on 12 September 2018.

The full PAR for Bimatoprost eye drops follows this summary.

This summary was last updated in November 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aspire Pharma Ltd, a Marketing Authorisation for the medicinal product for Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container (PL 35533/0128) on 12 September 2018.
This is a prescription only medicine (POM), indicated for reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

This application was submitted as abridged national application, according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The applicant has cross-referred to Lumigan 0.3 mg/ml eye drops, solution, single dose container, authorised to Allergan Pharmaceuticals Ireland through a centralised procedure (EU/1/02/205/005-007) on 08 March 2002 for the multi-dose container. Lumigan 0.3 mg/ml eye drops, solution in single-dose container was authorised in 2012 and belongs to the same marketing authorisation as the multi-dose container.

Bimatoprost is a potent ocular hypotensive agent. It is a synthetic prostamide, structurally related to prostaglandin F2α (PGF2α), that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified.

The mechanism of action by which bimatoprost reduces intraocular pressure in humans is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being hybrid medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence between the originator product ‘Lumigan 0.3 mg/ml, eye drops, solution, single-dose container’ and ‘bimatoprost 0.3 mg/ml, eye drops, solution, single-dose container’ cannot be demonstrated through bioavailability studies for locally acting products. A biowaiver was requested. The justification for a biowaiver is acceptable, in line with provisions of the guideline on investigation of bioequivalence.

The applicant has performed pharmaceutical equivalence testing to demonstrate equivalence in terms of the active content and assay of related substances (qualitative and quantitative composition).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as an eye drop solution and each ml contains 0.3 mg of bimatoprost, as active ingredient. The excipients present are sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium hydroxide or hydrochloric acid (for pH adjustment) and water for injection.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of sodium phosphate dibasic heptahydrate which complies with the United States. Pharmacopeia. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used in the product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in sachet containing 5 low density polyethylene single-dose containers containing 0.4 ml of solution.

The pack sizes are:
5 x 0.4 ml (1 sachet with 5 single dose containers)
30 x 0.4 ml (6 sachets with 5 single dose containers)
90 x 0.4 ml (18 sachets with 5 single dose containers)

Not all pack sizes may be marketed.

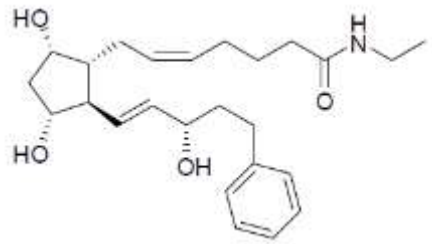
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: **Bimatoprost**

Chemical name(s): 5-Heptenamide, 7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-penten-1-yl]cyclopentyl]-N-ethyl-, (5Z)-

Structure:



Molecular formula: $C_{25}H_{37}NO_4$
Molecular weight: 415. g/mol
Appearance: Bimatoprost is a white or almost white crystalline powder.
Solubility: Bimatoprost is very soluble in ethanol and slightly soluble in water.

Bimatoprost is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, bimatoprost, are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a stable eye drop solution in single container that could be considered as a hybrid medicinal product of the currently licensed product, Lumigan 0.3 mg/ml eye drops, solution, single dose container (Allergan Pharmaceuticals Ireland).

The physicochemical properties of the proposed product versus the reference product have shown that the products are comparable.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months for unopened sachet with a storage condition ‘Keep the single-dose containers in the original package in order to protect from light’ has been set. Once the sachet is opened, the single-dose containers must be used within 7 days. The opened single-dose container must be discarded immediately after use.

The proposed shelf-life and storage condition are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of bimatoprost are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

No new non-clinical pharmacology studies have been submitted and none are required for this type of application. The non-clinical overview provides an adequate review of available literature data on the pharmacology of bimatoprost.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetics studies have been submitted and none are required for this type of application. The non-clinical overview provides an adequate review of available literature data on the pharmacokinetics of bimatoprost.

III.4 Toxicology

No new non-clinical toxicity studies have been submitted and none are required for this type of application. The non-clinical overview provides an adequate review of available literature data on the toxicology of bimatoprost.

III.5 Environmental Risk Assessment (ERA)

Since Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container is intended for generic substitution, its use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of bimatoprost are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

Systemic absorption of bimatoprost after topical administration of 0.3mg/ml eye drops has been shown to be negligible (generally below the limit of detection) with no significant systemic drug accumulation over time.

The conjunctiva does not appear to present a significant permeability barrier to bimatoprost and data indicated that the sclera provided direct access for bimatoprost into intraocular target tissues such as the ciliary body and trabecular meshwork with relatively little penetration into the aqueous humour.

In accordance with the guidance on 'The clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95/final) and the 'Note for guidance on the investigation of bioavailability and bioequivalence', no bioavailability, pharmacodynamics, or comparative clinical studies have been performed with the test product which is a locally applied, locally acting, ophthalmic solution. A biowaiver was requested. The justification for a biowaiver is acceptable, in line with provisions of the guideline on investigation of bioequivalence.

The test product is pharmaceutically equivalent to the reference product as it contains the same amount of the same active substance in the same dosage form.

IV.3 Pharmacodynamics

The pharmacodynamics of bimatoprost are well established and no new studies have been conducted and none are required for this type of application. The proposed product information provides the same relevant information as for the reference product, Lumigan 0.3 mg/ml eye drops, solution, single dose

container.

Bimatoprost is a prostaglandin F (PGF)-2α analogue which reduces IOP by increasing aqueous humor outflow by improving the two outflow pathways:

- pressure-dependent pathway (presumed trabecular, via Schlemm's canal and the episcleral veins)
- pressure independent pathway (presumed uveoscleral, ciliary muscle).

There is evidence that its actions are mediated via a novel prostamide-sensitive receptor at distinct cellular targets which could explain reported efficacy in latanoprost resistant patients.

IV.4 Clinical efficacy

No new studies have been conducted and none are required for this type of application. Treatment for glaucoma involves risk factor modification by amelioration of raised intraocular pressure (IOP) and the clinical efficacy of 0.3mg/ml bimatoprost eye drops, in reducing IOP, is well established. The aim is to reduce IOP to a target level considered to be sufficient to halt the progression of pathological ocular changes.

IV.5 Clinical safety

The clinical safety of Bimatoprost Aspire 0.3mg/ml eye drops in the proposed indication is well established. The clinical overview adequately summarises this and the proposed product literature, which is consistent with that of the reference product, adequately covers the known safety profile of bimatoprost eye drops and any potential undesirable effects.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Iris pigmentation	SmPC sections 4.4, 4.8 and 5.3 PIL sections 2 and 4 Prescription only medicine	None proposed
Acute asthma and asthmatic symptoms	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Choroidal effusion	SmPC section 4.8 Prescription only medicine	None proposed

Increase in intraocular pressure	SmPC section 4.4 and 4.5 PIL section 2 Prescription only medicine	
Reactivation of previous infective ocular disease	SmPC sections 4.4 and 4.8 PIL section 4 Prescription only medicine	None proposed
Cardiovascular events (bradycardia, angina & hypotension)	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None proposed
Off-label use (cosmetic use for stimulation of eyelash growth)	SmPC sections 4.1, 4.4 and 4.8 PIL sections 1 and 4 Prescription only medicine	None proposed
Use during pregnancy and lactation	SmPC section 4.6 PIL section 2 Prescription only medicine	None proposed
Paediatric use	SmPC sections 4.2 and 5.1 PIL section 2 Prescription only medicine	None proposed

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Bimatoprost 0.3mg/ml eye drops, solution (PL 35533/0106). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with bimatoprost is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for Bimatoprost Aspire 0.3mg/ml eye drops, solution in single-dose container is provided below:


Bimatoprost
0.3mg/ml eye drops, solution
in single-dose container
Preservative free
1ml of solution contains 0.3mg of bimatoprost.
Excipients: Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium hydroxide or hydrochloric acid (for pH adjustment), water for injections.
Ocular use. Read the package leaflet before use.
Keep out of the sight and reach of children.
For single use only.
Once the sachet is opened, use the single-dose containers within 7 days.
Keep single-dose containers in the original package in order to protect from light.
Discard the opened single-dose container immediately after use.
MA Holder:
Aspire Pharma Limited
Unit 4, Rotherbrook Court, Bedford Road, Petersfield
Hampshire, GU32 3QG, UK
POM PL 35533/0128 oooooo-S2.1
5 single-dose containers
Lot:
Exp:

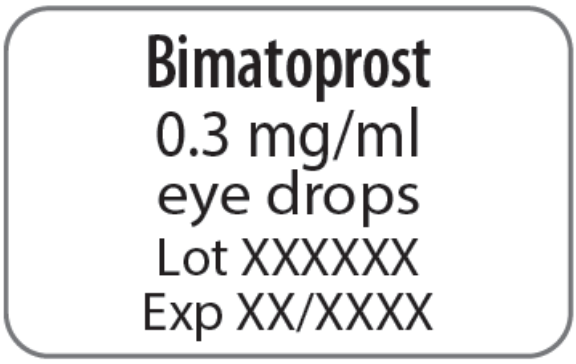

Bimatoprost
0.3 mg/ml
eye drops
Lot XXXXXX
Exp XX/XXXX

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome